Hepatic progenitor cells (HPC) are a bipotent cell population of the liver that may differentiate towards hepatocytes or cholangiocytes (1-3). HPC are mostly quiescent in normal livers while proliferate following liver injury. The activation of HPC results in mature hepatocytes or mature cholangiocytes or, in case of chronic damage, in the appearance of “reactive” cholangiocytes (2,3). The latter are small cells positive for cytokeratin 7 and 19 that try to form new ducts but result in clusters that not encircle a well-defined lumen. This reactive process that, in human livers, is mainly localized at the interface between the portal and parenchymal compartments is called ductular reaction” (DR) (4). DR is a well-known reparative mechanism of the liver and several studies have shown how these reparative mechanisms recapitulate developmental liver morphogenetic processes (3,5-8). Reparative processes are different between biliary and hepatocellular diseases, and involve different signaling mechanisms, for example Notch (9-11) or Wnt (12) for biliary or hepatocellular specification, respectively. Reactive cholangiocytes are often confused with hepatic progenitor cells; in fact, the evidence that reactive cholangiocytes are bipotential is scant. In chronic conditions, reactive cholangiocytes correlate with fibrosis and disease progression, indicating that they are the result of pathologic, rather than physiologic repair (3). In fact, “reactive” cholangiocytes re-expresses growth factors, transcription factors and morphogens enabling an active cross-talk between biliary, mesenchymal, vascular and inflammatory cells (3,6). Among these factors, vascular endothelial growth factor (VEGF) and angiopoietins have drawn considerable attention (5,13,14).

VEGF is a complex system of six different factors: VEGF-A, -B, -C, -D and -E and placenta growth factor. Together with its receptors VEGFR1 (Flt-1), VEGFR2 (Flk-1), VEGFR3 (Flt-4) and angiopoietins, VEGF is involved in the regulation of vascular growth, permeability, migration and survival of endothelial cells (15). Although originally thought to be restricted to vascular cells, recent studies have shown that VEGF, together with its receptors, is expressed and functional also in epithelial cells. In particular, in cholangiocytes, VEGF-A appears to regulate VEGF regulate cell proliferation and cross-talk during development, as well as in normal and diseased conditions (3,5,13,16-18). During liver development, VEGF is a key signal, able to link bile ducts and the network of capillaries emerging from the finest branches of the hepatic artery known as peribiliary plexus (PBP) (13). In fact, the developing bile ducts produce VEGF-A which in turn acts on endothelial cells and their precursor to promote arterial and PBP vasculogenesis (13). Similarly, in ductal plate malformations (DPM), the dysmorphic bile ducts actively secrete VEGF-A and are surrounded by an increased number of vascular structures (19). This is particular evident in cystic cholangiopathies where, in addition to secreting VEGF-A the biliary epithelium expresses VEGFR-2 receptor, that respond to VEGF by increasing proliferation and cyst growth (13). Studies in animal models of Autosomal Dominant Polycystic Kidney Disease (ADPKD) indicate that VEGF stimulates the progression of liver cysts in via autocrine stimulation of cholangiocytes proliferation and paracrine induction of pericycstic angiogenesis (17,18). In fact, VEGF induces cell proliferation through the activation of PKA/ERK1/2 signaling, the most important proliferative pathway in cholangiocytes. In turn, an altered cAMP/PKA/
ERK1/2 signaling is responsible of the increased hypoxia-inducible factor 1 α-mediated VEGF secretion (16-18). The blockade of this signaling using inhibitors of VEGFR-2 or mTOR or cAMP production resulted in a significantly decreased in cyst growth (17,18).

In this issue of Hepatobiliary Surgery and Nutrition, Franchitto and colleagues shows that in chronic liver diseases, such as primary biliary cirrhosis (PBC) and HCV-related cirrhosis, VEGF is expressed in HPC and ductular reactive cells (20). In particular, the results show that expansion of HPC is more extensive in PBC with respect to HCV samples. PBC samples were also characterized by a more extensive angiogenesis and by an increased expression of VEGF-A and VEGF-C and VEGF receptors. Moreover, the average number of HPC expressing VEGFs was higher in samples with more extensive ductular reaction and angiogenesis. These findings are of interest because they are consistent with the idea that a VEGF-mediated cross talk between HPC/DR and endothelial cells may be involved in the remodeling of the vascular bed occurring in ductular reaction. The increased nutritional and functional demand is supported with changes in vascular architecture mediated by an increased secretion of VEGF. Furthermore, in PBC samples, reactive ductules were closer to fibrous septa and strands of ductular reactive cells penetrated in the cirrhotic nodules stimulating the formation of new vessels within fibrous septa. Interestingly, previous studies have shown that VEGF, released at the leading or lateral edge of developing fibrous septa, recruits activated hepatic stellate cells (HSC), which express VEGFR-1 and VEGFR-2 (21). In addition, in vitro experiments have shown that HSC migration was VEGFR-2-dependent through the activation of the Ras/ERK pathway. Furthermore, other studies have shown that in vivo administration of VEGFR-2 neutralizing antibody reduced neovascularization as well as fibrosis and the number of α-SMA positive cells in the chronic model of CCL_4-induced fibrosis (22).

Franchitto et al. did not find immunohistochemical evidence of VEGFR-2 expression in hepatic progenitor cells/oval cell. Unfortunately, the criteria used to distinguish HPC from reactive ductular cells remained unclear. Several studies in humans and rodent have shown that VEGFR-2 is expressed in reactive cholangiocytes. Strong expression of VEGFR-2 in cholangiocytes was reported in biliary atresia (23,24), in ischemia/reperfusion damage (25) in chronic alcoholic liver disease (26), as well as in developing ductal plates (5). Furthermore, VEGFR-2 is expressed in cholangiocytes, in several animal models of cholangiopathies (17,18,22) both in vitro and in vivo. After administration of VEGF, VEGFR-2 is phosphorylated and induces cholangiocytes proliferation through the activation of the MEK/ERK1/2 pathway (12,13,19).

In conclusion, this study is consistent with the idea that VEGF is a major factor in liver repair through an autocrine effect on HPC/DR cell proliferation and a paracrine effect on surrounding endothelial cells. Exploring the complex interactions of HPC with surrounding inflammatory, mesenchymal and in the case of this study with endothelial cells will further enhance our understanding of physiologic and pathologic liver repair and, thereby, lead to new therapeutic possibilities.

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**References**
